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Filed : May 2, 2002

## REMARKS

Applicants thank the Examiner for her review of the instant application. Claims 1-5 remain present for examination. For the reasons stated below, the rejections of the presently pending claims are respectfully traversed.

### Priority

The PTO has stated that the subject matter defined in the present application is not supported by the disclosure in any of the applications for which Applicants claim priority because the claimed subject matter does not have utility, enablement, or written description. The PTO therefore sets the priority under 35 U.S.C. §120 to the instant filing date, May 2, 2002.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. §120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. §120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. §120 to, US Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. §371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. §119 to US Provisional Application 60/096959 filed 8/18/1998.

The sequence of SEQ ID NO:38 was first disclosed in US Provisional Application 60/096959 filed 8/18/1998 in Figure 2 and SEQ ID NO:2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed antibodies, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. For the reasons detailed below, Applicants submit they are entitled to at least the priority date of August 24, 2000.

### Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of pending Claims 1-5 under 35 U.S.C. § 101 as lacking utility for the reasons set forth in the previous Office Action. Briefly stated, the PTO argues that the relied upon utility specifically requires or constitutes carrying out further research to identify

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or reasonably confirm a "real world" context of use and as such is therefore not a "substantial utility."

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the PTO has not met its burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However even if the PTO has met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability**, that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

## Substantial Utility

### Summary of Applicants' Arguments and the PTO's Response

Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1344 polypeptide is more highly expressed in normal stomach, normal skin and kidney tumor tissue than in stomach and melanoma tumor, and normal kidney, respectively;
2. Applicants assert that it is well-established in the art that a **change** in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a **corresponding change** in the level of the encoded protein, e.g. a decrease;
3. Given Applicants' evidence that the mRNA for the PRO1344 polypeptide is differentially expressed in stomach, melanoma and kidney tumors compared to normal stomach, skin and kidney tissue, respectively, it is more likely than not that the PRO1344 polypeptide is differentially expressed in stomach, melanoma and kidney tumors compared to normal stomach, skin and kidney tissue, respectively, making the claimed antibodies that specifically bind to the

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differentially expressed PRO1344 polypeptide useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making essentially two arguments in response to Applicants' asserted utility:

1. The PTO has argued that further details regarding Example 18 are required;
2. The PTO continues to rely on Pennica *et al.*, Hu *et al.*, Haynes *et al.*, Konopka *et al.*, Lewin (Genes VI), Gokman-Polar *et al.* as well as newly cited references by Chen *et al.* (Mol. and Cell. Proteomics, (2002) 1:304-313), Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30), and Anderson and Seilhamer (Electrophoresis 1997; 18:533-37) to support its assertion that gene amplification is not correlated with mRNA levels, and mRNA levels are not correlated with polypeptide levels. Therefore, the specification "provides a mere invitation to experiment for establishing a specific and substantial use for the claimed antibodies that bind the polypeptide of SEQ ID NO:38, which does not reasonably extrapolate to a readily available utility." *Final Office Action* at 17.

Applicants respectfully submit that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

*The Report by Hu et al. is Irrelevant to Applicants' Asserted Diagnostic Utility*

The PTO cites Hu *et al.* as evidence of a lack of utility. The PTO states that "Hu et al was cited to provide evidence that one skilled in the art would not more likely than not believe that a change less than five fold would be indicative of a role in cancer as it related to the allegations of utility with respect to therapeutics and gene therapy." *Final Office Action* at 5. The PTO thus concludes that Hu establishes Applicants' claimed antibodies do not have a therapeutic utility. The PTO is silent regarding any teaching by Hu that would be relevant to a diagnostic utility for the claimed antibodies. Thus, while Applicants take no position regarding the implication of Hu's teachings on the therapeutic utility of the claimed antibodies, it is clear that Hu has no bearing whatsoever on Applicants' asserted diagnostic utility for the claimed antibodies.

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In addition to these and the reasons previously articulated in Applicants' arguments of record, the PTO's reliance on Hu is also misplaced because Applicants are not relying on microarray data as discussed in Hu:

In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study. *Hu* at 405, left column, first paragraph (emphasis added).

Instead, Applicants are relying on a more accurate and reliable method of assessing changes in mRNA level, namely quantitative PCR analysis. In a recent study by Kuo *et al.*, (Proteomics 5(4):894-906 (2005)), the authors used microarray analysis combined with proteomic analysis using two-dimensional gel electrophoresis to examine changes in gene expression in leukemia cell lines. The authors report that “[c]omparison of microarray and proteomic expression profiles showed poor correlation. Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction [RT-PCR], Western blotting and functional assays, on several genes and proteins, nonetheless, confirmed that there is indeed good correlation between mRNA and protein expression.” *Kuo et al.* at Abstract (emphasis added) (attached as Exhibit 1). Thus, even if accurate, Hu's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

*The Data Reporting Differential Expression of PRO1344 mRNA is Sufficient to Provide Utility for the mRNA as a Diagnostic Tool*

Applicants submit that the PTO's position that additional details regarding Example 18 – such as the number of samples tested, the numerical values of expression, or whether the results are statistically significant – are required to establish utility for the claimed antibodies is beyond that required under 35 U.S.C. §101. Applicants' statement of utility is presumed to be true, and further evidence to establish utility should not be required. *See In re Langer*, 503 F.2d at 1391, 183 USPQ at 297; *In re Malachowski*, 530 F.2d 1402, 1404, 189 USPQ 432, 435 (CCPA 1976); *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); *M.P.E.P.* §2107.02 (III). Requests for additional evidence should be imposed rarely, such as only when a statement is incredible in the light of the knowledge of the art, or factually misleading. *In re Citron*, 325 F.2d 248, 139 USPQ 516 (CCPA 1963); *M.P.E.P.* §2107.02 (V). In addition, as stated above, the standard for establishing a utility is a low one, and statistical certainty is not required:

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[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true “beyond a reasonable doubt.” **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The Federal Circuit has clearly rejected a requirement that evidence of utility be numerically precise or statistically significant. In *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. 881 (C.C.P.A. 1980), the issue in the interference was whether Nelson had shown at least one utility for the compounds at issue to establish an actual reduction to practice. *Id.* at 855. The Appellants relied on two tests to prove practical utility: an *in vivo* rat blood pressure (BP) test and an *in vitro* gerbil colon smooth muscle stimulation (GC-SMS) test. In the BP test, responses were categorized as either a depressor (lowering) effect or a pressor (elevating) effect. *Id.* The Board held that Nelson had not shown adequate proof of practical utility, characterizing the tests as “rough screens, uncorrelated with actual utility.” *Id.* at 856.

On appeal the C.C.P.A. reversed, holding that the Board “erred in not recognizing that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use.” *Id.*

Bowler argued that the BP and GC-SMS tests were inconclusive showings of pharmacological activity since confirmation by statistically significant means did not occur until after the critical date. The Court rejected this argument, stating that “a rigorous correlation is not necessary where the test for pharmacological activity is reasonably indicative of the desired response.” *Id.* (emphasis added). The Court concluded that a “reasonable correlation” between the observed properties and the suggested use was sufficient to establish practical utility. *Id.* at 857 (emphasis added).

This case is of importance because the Court rejected the notion that the testing must be statistically significant to support a practical utility. *Nelson*, 626 F.2d at 857. Likewise, qualitative characterizations of a test compound as either increasing or decreasing blood pressure was acceptable. *Id.* at 855 (stating that responses were categorized as either a depressor (lowering) effect or a pressor (elevating) effect). This is the same as the data in Example 18 relied on by Applicants, where the change in mRNA levels is described as “more highly

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expressed.” The PTO’s requirement that Applicants provide numerical precision and statistical certainty to establish utility is contrary to established standards for utility. Thus, these arguments do not support the PTO’s position as they do not lead one skilled in the art to question Applicants’ asserted utility.

In asserting that Applicants’ disclosure of differential expression of the PRO1344 mRNA is insufficient, the PTO states that the specification does not “provide any evidence that indicates what the differences were or if they were statistically significant.” *Final Office Action* at 8. Thus, the PTO has set a heightened requirement for Applicants to demonstrate utility based on the disclosed differential expression. Moreover, the PTO fails to support this heightened requirement with any evidence. The PTO provides no evidence or findings of facts to suggest that one skilled in the art would doubt Applicants’ disclosed differential expression. Applicants submit that the PTO’s requirement for statistically significant evidence is improper and insufficient to overcome Applicants’ presumption of utility.

Notwithstanding the presumption of utility that should be accorded to Applicants’ claimed antibodies, Applicants previously submitted a copy of a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. As discussed previously, the declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue.

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest “can be used to differentiate tumor from normal,” and that the samples were made from pooled samples of tumor and corresponding normal tissue, increasing the accuracy of the data, thus establishing their reliability. *See Grimaldi Declaration* at ¶¶ 5 and 7.

In addition, he explains that, contrary to the PTO’s assertions, “[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression

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between normal tissue and tumor tissue.” *Grimaldi Declaration* at ¶7. Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant, as is the baseline level of expression. As Mr. Grimaldi states, “[i]f a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor.” *Id.*

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that “[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned.” *PTO Utility Examination Guidelines* (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as “opinions” without an adequate explanation of how the declaration fails to rebut the PTO’s position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

In conclusion, Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establishes that there is at least a two-fold difference in PRO1344 mRNA between stomach, skin and kidney tumors compared to their respective normal tissue counterparts. The PTO has not offered any evidence or significant arguments to the contrary, and therefore any challenge to the sufficiency of the data with respect to the utility of the nucleic acid is inappropriate. Thus, the only issue which remains is whether the data in Example 18 regarding differential expression of the PRO1344 mRNA are reasonably correlated with differential expression of the PRO1344 polypeptide such that the claimed antibodies that specifically bind to the PRO1344 polypeptide can be used to distinguish normal tissue from its cancerous counterpart. As discussed below, even if the PTO has established a reasonable doubt regarding Applicants’ assertion that they are reasonably correlated, Applicants’ overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level more often than not lead to corresponding changes in protein level.

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The PTO's Evidence is Not Relevant to Determining Whether a Change in mRNA Level for a Particular Gene leads to Corresponding Change in the Level of the Encoded Protein

Applicants turn next to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1344 polypeptide in stomach, skin and kidney tumors, it is likely that the PRO1344 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors, and antibodies that bind these proteins, have utility as diagnostic tools.

In response to Applicants' assertion, the PTO relies on Pennica *et al.*, Haynes *et al.*, Konopka *et al.*, Lewin (Genes VI), Gokman-Polar *et al.* as well as newly cited references by Chen *et al.*, Gygi *et al.*, and Anderson and Seilhamer.

Applicants have previously discussed at length why the Pennica *et al.*, Haynes *et al.*, Konopka *et al.*, Lewin (Genes VI), Gokman-Polar *et al.* references are not relevant to the issue of whether changes in mRNA level for a particular gene lead to changes in protein level. Briefly stated, references such as Pennica and Konopka which the PTO cites to teach that gene copy number does not equate with mRNA number are not relevant because Applicants do not rely on any relationship between gene copy number and mRNA levels. Likewise, references such as Haynes, Gygi, Anderson, and portions of Chen which discuss the correlation between static levels of mRNA and static levels of protein across different genes are also not relevant – Applicants rely only on the assertion that changes in mRNA level generally lead to corresponding changes in the encoded protein level. Applicants incorporate by reference the previous arguments made regarding these issues, and will not repeat them here.

However, Applicants offer the following in an attempt to clarify the basis for Applicants' distinguishing the cited references. Haynes, Gygi, Anderson, and portions of Chen attempted to discover a global ratio common between all steady state mRNA levels and all steady state protein levels. The data of Haynes, Gygi, Anderson, and portions of Chen indicated that the steady state ratio of mRNA level:protein level varied for different genes, and hence no global ratio existed. Based on this, the references concluded that protein levels cannot be accurately calculated from mRNA levels.

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In contrast, Applicants' assertions require no knowledge of a ratio between mRNA levels and protein levels, nor do Applicants' assertions require calculation of protein levels based on measured mRNA levels. Applicants simply assert that a change in mRNA level for a particular gene typically leads to a corresponding change in the encoded protein level. *See, e.g., First Grimaldi Declaration* at paragraph 7. Haynes, Gygi, Anderson, and portions of Chen were concerned with a different question, and, therefore, none of the data or conclusions of these references has any bearing on Applicants' assertions.

Further regarding Chen *et al.*, this reference reported that plotting the level of mRNA for a particular gene against the level of the corresponding protein as measured across numerous samples, they found a lack of correlation for most genes studied. *Chen* at Abstract. However, with the exception of three genes reported in Figures 2A-2C, Chen does not indicate whether the level of mRNA varied significantly across samples, and Chen did not select samples or genes which were expected to vary across samples (e.g. normal versus tumor). Therefore, it is not known if Chen examined changes in mRNA level, or if the level of mRNA was unchanged. Therefore, the relevance of Chen's finding to Applicants' asserted correlation between changes in mRNA and protein is not known.

In conclusion, Applicants have shown that the Haynes, Gygi, Anderson, and Chen references are simply not relevant to the issue of whether a change in mRNA levels leads to a corresponding change in the level of the encoded protein. As such, the PTO's arguments are not sufficient to satisfy the burden to "provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

According to the Examiner, the lack of correlation between mRNA and protein levels is confirmed by Gokman-Polar *et al.* (Cancer Research 61:1375-1381, 2001) that indicates the absence of a correlation between increased mRNA levels and increased protein levels. With respect to the Gokman-Polar reference, the PTO points to Figures 6 and 7 as showing that "an apparent at least two-fold difference in QRT-PCR products, does not correspond to similar difference in [sic] protein production." *Final Office Action* at 12. However, a review of the entire article indicates that with one exception, the trend in the data is that mRNA and protein levels are positively correlated, supporting Applicants assertion that increased mRNA levels

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correlate with increased protein levels. In Figure 2, the protein level of two isozymes shows a decrease, while the third is increased. This same pattern is seen for the corresponding mRNA levels in Figure 6, although admittedly the increase in mRNA for the third isozyme is small. Similarly, comparing the protein levels of the three isozymes in Figure 4 to the corresponding mRNA levels in Figure 7, with one exception the mRNA levels are positively correlated to protein levels. While protein levels do not increase or decrease in direct proportion to the changes in mRNA, the trend in five of the six examples is that protein levels are positively correlated to mRNA levels. This evidence is hardly sufficient to establish that one of skill in the art would reasonably doubt that there is a reasonable correlation between mRNA levels and protein levels.

The Examiner also cites the textbook by Lewin as supporting the conclusion that one skilled in the art would not assume that small increase/decrease in mRNA would correlate with corresponding changes in polypeptide levels. As Applicants have previously cited Lewin states, “having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription.” *Genes VI* at 847-848 (emphasis added). Further, Lewin goes on to state that transcription of a gene “is a major control point: probably it is the most common level of regulation.” *Id.*, emphasis added. This reference provides additional support for Applicants’ position that that the accepted understanding in the art is that there is a *reasonable* correlation between gene expression and the level of the encoded protein. Applicants do not assert that protein expression is never regulated at the translation level (*i.e.*, post-transcriptionally), but rather that, more often than not, regulation of protein expression occurs at the transcriptional level, making the level of mRNA a general indicator of the level of protein, and, more particularly, making changes in the level of mRNA a general indicator of changes in the level of protein. Far from rebutting this assertion, Lewin in fact supports it by stating that regulation occurs at the transcriptional stage in the overwhelming majority of cases, and that transcription is the most common level of regulation.

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Applicants' Evidence Establishes that a Change in mRNA Level for a Particular Gene lead to a Corresponding Change in the Level of the Encoded Protein

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, a copy of the declaration of Paul Polakis, Ph.D., excerpts from the Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3<sup>rd</sup> ed. 1994) and (4<sup>th</sup> ed. 2002), excerpts from the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)), a reference by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, and a reference by Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002). The details of the teachings of these declarations and references, and how they support Applicants' asserted utility, are of record and will not be repeated here.

In addition to the supporting references previously submitted by Applicants, Applicants submit the following references to further support the assertion that changes in mRNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

In a comprehensive study by Orntoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45) (previously submitted with IDS, attached hereto as Exhibit 2), the authors examined gene amplification, mRNA expression level, and protein expression in pairs of non-invasive and invasive human bladder tumors. *Id.* at Abstract. The authors examined 40 well resolved abundant known proteins, and found that “[i]n general there was a highly significant correlation ( $p<0.005$ ) between mRNA and protein alterations. Only one gene showed disagreement between transcript alteration and protein alteration.” *Id.* at 42, col. 2. The alterations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

In a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 3) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that “[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin

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and beta-catenin mRNA were also observed.” *Id.* As Applicants’ assertion would predict, the authors state that the mRNA measures showed “good correlation” with the results from protein measures. The authors conclude by stating that “this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied.” *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 4) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinases (MMPs). In the present study, the authors “used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in 20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels.” *Id.* Thus, the results support Applicants’ assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 5) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, “[s]ix of the seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal.” *Id.* The authors conclude that the study “demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein.” *Id.* Thus, this reference supports Applicants’ assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 6) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further

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understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. “Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/- 2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20S $\alpha$  subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis.” These findings support Applicants’ assertion that changes in mRNA level lead to changes in protein level.

Maruyama *et al.* (Am. J. Patho. 1999; 155(3):815-22) (abstract attached as Exhibit 7) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that pancreatic cancer cell lines frequently coexpressed all three Ids, “exhibiting good correlation between Id mRNA and protein levels.” *Id.* at Abstract. In addition, the authors teach that all three Id mRNA levels were expressed at high levels in pancreatic cancer samples compared to normal or CP samples. At the protein level, Id-1 and Id-2 staining was faint in normal tissue, while Id-3 ranged from weak to strong. In contrast, in the cancer tissues “many of the cancer cells exhibited abundant Id-1, Id-2, and Id-3 immunoreactivity,” and Id-1 and Id-2 protein was increased significantly in the cancer cells by comparison to the respective controls, mirroring the overexpression at the mRNA level. Thus, the authors report that in both cell lines and tissue samples, increased mRNA levels leads to an increase in protein overexpression, supporting Applicants’ assertion.

Support for Applicants’ assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 8). In a previous study, the authors investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that “[t]he results demonstrate a good

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correlation between NPY peptide and mRNA expression.” Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Mizrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 9) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrous/estrous, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that “[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55 kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR.” *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants’ assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 10), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that “[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder.” *Id.* This report supports Applicants’ assertion that changes in mRNA level, e.g. a decrease, lead to a corresponding change in the level of the encoded protein, e.g. a decrease.

In an article by Guo and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 11) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome(ARDS) by examining the expression of MIF mRNA and protein in lung tissue in ARDS and normal persons. *Id.* at

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Abstract. The authors report “undetectable or weak MIF mRNA and protein expression in normal lungs. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lungs.” *Id.* This is consistent with Applicants’ assertion that a change in mRNA for a particular gene, e.g. an increase, generally leads to a corresponding change in the level of protein expression, e.g. an increase.

These studies are representative of numerous published studies which support Applicants’ assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit herewith an addition 70 references (abstracts attached as Exhibit 12) which support Applicants’ assertion.

In addition to these supporting references, Applicants also submit herewith additional references which offer indirect support of Applicants’ asserted utility. As discussed in detail above, Applicants have challenged the relevance of references such as Haynes *et al.*, Gygi *et al.*, Anderson *et al.*, and Chen *et al.* which do not attempt to examine the correlation between a change in mRNA level and a change in the level of the corresponding protein level. Because the PTO continues to rely on these references, Applicants are submitting references which report results that are contrary to the PTO’s cited references and offer indirect support for Applicants’ asserted utility.

For example, in an article by Futcher *et al.* (Mol. Cell Biol. 1999; 19(11):7357-68) (abstract attached as Exhibit 13) the authors conducted a study of mRNA and protein expression in yeast which was nearly identical to the one conducted by Gygi *et al.* and reported in Haynes *et al.* Contrary to the results of the earlier study by Gygi, Futcher *et al.* report “a good correlation between protein abundance, mRNA abundance, and codon bias.” *Id.* at Abstract.

In a study which is more closely related to Applicants’ asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 14) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that “there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied.” *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Similarly, in an article by Papotti *et al.* (Virchows Arch. 2002; 440(5):461-75) (abstract attached as Exhibit 15) the authors examined the expression of three somatostatin receptors

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(SSTR) at the mRNA and protein level in forty-six tumors. *Id.* at Abstract. The authors report a “good correlation between RT-PCR [mRNA level] and IHC [protein level] data on SSTR types 2, 3, and 5.” *Id.*

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 16) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that “enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels” and that there was a “good correlation between the different dCK measurements in malignant cells and tumors.” *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 17) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that “[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression.” *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 18) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC) B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that “GC cells had low expression commensurate with the low protein expression level” and that in DLBCL the level of BCL2 mRNA and protein expression showed “in general, a good correlation.” *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 19) the authors report that six mantle cell lymphomas studied “expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases).” *Id.* at Abstract. “There was a good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis.” *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO’s arguments. Applicants submit herewith 26 additional references (abstracts attached as Exhibit 20) which also support Applicants’ assertion in that the references report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

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In summary, Applicants submit herewith a total of 113 references in addition to the declarations and references already of record which support Applicants' asserted utility, either directly or indirectly. These references support the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.*, abstracts attached as Exhibit 21). However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P. at § 2107.02, part VII (2004).* Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

Applicants also previously submitted the Declaration of Paul Polakis in support of their position that in general, changes in mRNA levels correlate with changes in protein levels. In response to the Polakis Declaration, the PTO argues that "the declaration does not provide data such that the examiner can independently draw conclusions..." that increased mRNA levels are predictive of corresponding levels of the encoded polypeptide. *Final Office Action* at 14.

Without acquiescing to the propriety of this rejection, and merely to expedite prosecution in this case, Applicants submit herewith as Exhibit 22 a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions.

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The case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. In re Rinehart, 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and In re Piasecki, 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). “After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument” In re Alton, 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996)(quoting In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in In re Alton, “We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner” Id. at 1583. Applicants also respectfully draw the PTO’s attention to the Utility Examination Guidelines which state, “Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered.” Part IIB, 66 Fed. Reg. 1098 (2001).

In conclusion, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1344 mRNA is differentially expressed in stomach, skin and kidney tumors compared to their normal tissue counterparts, the PRO1344 polypeptide will likewise be differentially expressed in stomach, skin and kidney tumors. This differential expression of the PRO1344 polypeptide makes the claimed antibodies that specifically bind to the PRO1344 polypeptide useful as diagnostic tools for cancer, particularly stomach, skin and kidney cancer.

### Specific Utility

#### The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO’s assertion that the asserted utilities are not specific to the claimed antibodies that specifically bind to the PRO1344 polypeptide. Applicants respectfully disagree.

Specific utility is defined as utility which is “specific to the subject matter claimed,” in contrast to “a general utility that would be applicable to the broad class of the invention.” M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the

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PRO1344 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies that specifically bind to the PRO1344 polypeptide.

As discussed above, there are significant data which show that the gene for the PRO1344 polypeptide is differentially expressed in normal skin tissue, normal stomach tissue and normal kidney tissue compared to melanoma, stomach tumor and kidney tumor, respectively. These data are strong evidence that the PRO1344 gene and polypeptide are associated with stomach, skin and kidney tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1344 gene and polypeptide with a specific disease. The asserted utility for the claimed antibodies as diagnostic tools for cancer, particularly stomach, skin and kidney tumors, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

### **Utility – Conclusion**

Applicants remind the PTO that the evidence supporting utility does not need to be direct evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is “reasonably” correlated with the asserted utility is sufficient. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) (“a ‘rigorous correlation’ need not be shown in order to establish practical utility; ‘reasonable correlation’ suffices”); *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (same); *Nelson v. Bowler*, 626 F.2d 853, 857, 206 U.S.P.Q. 881 (C.C.P.A. 1980) (same). In addition, utility need only be shown to be “more likely than not true,” not to a statistical certainty. *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

### **Rejections under 35 U.S.C. § 112, first paragraph – Enablement**

The PTO also maintains its rejection of pending Claims 1-5 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by

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either a specific or substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. *Final Office Action* at 18.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

### **Rejection Under 35 U.S.C. §102**

Claims 1-5 are rejected under 35 U.S.C. §102(b) as being anticipated by Barnes et al. (WO 00/18904, published April 6, 2000). The PTO states that Barnes discloses a polypeptide that is 91.3% identical to SEQ ID NO:38, and that Barnes also teaches antibodies that bind this disclosed polypeptide. The PTO concludes that since the polypeptide of Barnes contains portions of its sequence that are 100% identical to portions of SEQ ID NO:38, the antibodies of Barnes would necessarily and inherently bind the polypeptide of SEQ ID NO:38.

Applicants respectfully traverse. While Applicants do not concede that Barnes inherently discloses the claimed antibodies, Applicants submit that the point is moot because Barnes is not prior art to the claimed antibodies.

To be anticipated under 35 U.S.C. §102(b), the invention must be patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States. Applicants submit that Barnes is not prior art under 35 U.S.C. §102(b) because it was not published one year before the priority date for the claimed antibodies. The instant application is a continuation of, and claims priority under 35 U.S.C. §120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. §120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. §120 to, US Application 09/380137 filed 8/25/99, which is the National Stage filed under 35 U.S.C. §371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. §119 to US Provisional Application 60/096959 filed 8/18/1998. Applicants submit that for the reasons stated above, the claimed antibodies have a credible, substantial, and specific utility. The sequences of SEQ ID NOS: 37 and 38 were first disclosed in US Provisional

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Application 60/096959 filed 8/18/1998 in Figures 1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Barnes was published April 6, 2000. Thus, Barnes was not published at least one year earlier than the August 24, 2000 filing date of Application PCT/US00/23328, or the July 2, 1998 filing date of US Provisional Application 60/091628. The instant application is entitled to priority to both, and therefore Barnes cannot be cited as prior art against the instant application under 35 U.S.C. §102(b).

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

#### CONCLUSION

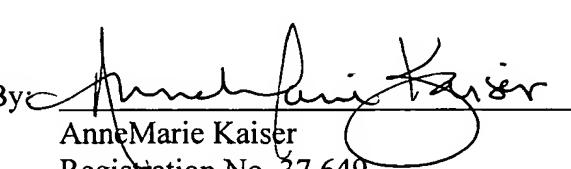
In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: June 26, 2006

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